REMARKS/ARGUMENTS

Claims 42 and 44-75 are pending in the above-referenced patent application and are currently under examination.

In the Office Action, the drawings have been objected to for the reasons set forth in the PTO-948 form. In addition, claims 42 and 44-75 remain rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Choi *et al.* For the reasons set forth herein, the foregoing objection to the drawings and § 102(e) rejection of claims 42 and 44-75 are overcome.

The Invention

Novel lipid-nucleic acid particles which are useful for *in vitro* or *in vivo* gene transfer are provided by the present invention. The particles can be formed using either detergent dialysis methods or methods that utilize organic solvents. Upon removal of a solubilizing component (*i.e.*, the detergent or the organic solvent), the lipid-nucleic acid complexes form particles, wherein the nucleic acid is serum-stable and is protected from nuclease degradation.

Objection to the Drawings

The drawings have been objected to for the reasons set forth in the PTO-948 form. In order to expedite prosecution, Applicants submit concurrently herewith in a separate paper drawings that overcome the objections set forth in the PTO-948 form. Accordingly, Applicants urge the Examiner to withdraw the objection to the drawings.

Rejection Under 35 U.S.C. § 102(e)

Claims 42 and 44-75 remain rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5, 820,873 ("Choi *et al.*"). In view of the following remarks, Applicants respectfully traverse the rejection.

> To anticipate a claim, a reference must disclose each and every element of the challenged claim and must enable one skilled in the art to make the anticipated subject matter.

See, *PPG Industries Inc. v. Guardian Industries Corp.*, 37 USPQ2d.

Claim 42 of the present invention is directed to a nucleic acid-lipid particle comprising a cationic lipid, a conjugated lipid that inhibits aggregation of particles, and a nucleic acid, ***wherein the nucleic acid in the nucleic acid-lipid particle is resistant in aqueous solution to degradation with a nuclease.***

As stated on page 4, lines 29-31, of the specification, the nucleic acid-lipid particles of the present invention are constructed in a way such that upon removal of a solubilizing component (*i.e.*, the detergent or the organic solvent depending on which methods is employed), the ***nucleic acid becomes protected from nuclease degradation***. The nucleic acid-lipid particles thus formed are suitable, *inter alia*, for use in intravenous nucleic acid transfer as they are stable in circulation, of a size required for pharmacodynamic behavior resulting in access to extravascular sites, and target cell populations.

Choi *et al.* teach a novel class of polyethylene glycol modified ceramide lipids, *i.e.*, PEG-ceramide conjugates, that can be used to form liposomes and other lipid formulations containing various biological agents or drugs.

In connection with the previously filed RCE Amendment, Applicants submitted the Declaration of Michael J. Hope, Ph.D. ("the Hope Declaration"), wherein after reviewing the teachings of the Choi *et al.* patent, Dr. Hope concluded that "the Choi *et al.* patent does ***not*** teach (or even suggest) the nucleic acid-lipid particles recited in claims 42 and 44-75 because Choi *et al.* do ***not*** teach (or even suggest) (1) nucleic acid-lipid particles, wherein the nucleic acid in the nucleic acid-lipid particles is resistant in aqueous solution to degradation with a nuclease, or (2) methods for making such nucleic acid-lipid particles" (*see*, paragraph 13 of the Hope Declaration). Despite Dr. Hope's conclusions, the Hope Declaration was found to be insufficient to overcome the § 102(e) rejection. As such, the Office Action continues to allege that the liposomes disclosed by Choi *et al.* produce particles that meet the structural limitations of the particles produced by the methods of the instant invention and are, therefore, presumed to have the same functional properties as the particles produced by the method of the present invention.

In order to further prosecution, Applicants submit concurrently herewith the Declaration of Sean Semple, M.Sc. ("the Semple Declaration") pursuant to 37 C.F.R. § 1.132.

As explained in the Semple Declaration, the Choi *et al.* patent discloses in the Example Section methods for loading therapeutic agents, *e.g.*, vincristine, into liposomes. Example 9 sets forth an example of such a loading (or encapsulation) method, wherein it states:

> The dry lipid was hydrated with 300 mM citrate buffer, pH 4.0. Following extrusion, the vesicles (100 mg/mL) were added to a solution of vincristine (Oncovin; 1 mg/ml) to achieve a drug:lipid ration of 0.1:1. The exterior pH of the liposome/vincristine mixture was raised to pH 7.0-7.2 by titration with 500 mM sodium phosphate and immediately the sample was heated to 60°C for 10 minutes to achieve encapsulation of the vincristine.

See, Example 9, column 21, lines 11-18. Example 10 sets forth a similar loading/encapsulation procedure for loading vincristine into liposomes (*see*, Example 10, column 21, line 62 through column 22, line 9).

As explained in the Semple Declaration, the loading/encapsulation methods disclosed in Choi *et al.* are useful for loading small molecules (*e.g.*, vinca alkaloids, *etc.*) into liposomes, but are not useful for loading nucleic acids (*e.g.*, oligonucleotides, plasmid DNA, *etc.*) into liposomes because nucleic acids do ***not*** readily cross intact lipid membranes. According to the Semple Declaration, if one were to use the loading/encapsulation methods disclosed in Choi *et al.* and were to add external plasmid DNA to preformed liposomes in aqueous buffer, one would ***not*** expect to see ***any*** entrapment of the plasmid DNA in the liposomes because, again, nucleic acids do ***not*** readily cross intact lipid membranes.

Moreover, as explained in the Semple Declaration, as of the filing date of the Choi *et al.* patent, *i.e.*, 1994-1995, the state-of-the-art was to prepare cationic liposomes and, then, to complex the preformed cationic liposomes with DNA in an aqueous solution to form DNA-cationic liposome complexes (*i.e.*, lipoplexes). According to the Semple Declaration, given that DNA does ***not*** readily cross lipid membranes and that the cationic lipids present in the external membrane of the vesicles would electrostatically interact with the negatively charged DNA, the mixing of DNA with preformed cationic liposomes in aqueous solution does ***not*** result in entrapment of DNA within the internal, aqueous space of the liposomes. According to the Semple Declaration, the lipoplexes formed by this proves are ill-defined, are only partially protected from nucleases, are heterogeneous

in size and are rapidly cleared from the circulation. In further support of this position, the Semple Declaration points to Figure 2 of Wheeler, *et al.*, *Gene Therapy*, 6:271-281 (1999); and Figure 1 of Monck *et al.*, *J. Drug Targeting*, 7:(6):439-452 (2000), copies of which are attached to the Semple Declaration as Exhibits B and C.

As such, it is Sean Semple's opinion that when Choi *et al.* state that cationic carriers of DNA can be improved through the addition of PEG lipids, such as the PEG-ceramide conjugates disclosed and claimed therein, Choi *et al.* are referring to the preformed cationic liposome carriers that are then complexed with DNA to form lipoplexes as described above. In further support of this position, the Semple Declaration points to the examples provided in Choi *et al.* wherein Choi *et al.* demonstrate that aggregation of the cationic liposomes alone (no DNA) can be inhibited in the presence of serum (most serum proteins carry a net negative charge) if the liposomes contain a PEG-ceramide conjugate.

According to the Semple Declaration, in contrast to the teachings of Choi *et al.*, the present invention provides novel methods by which nucleic acids (*e.g.*, oligonucleotides, plasmid DNA, *etc.*) are entrapped, *i.e.*, encapsulated, within individual cationic liposomes that include a conjugated lipid, such as a PEG-lipid conjugate. As explained in the specification and as set forth in the presently pending claims, the PEG-lipid conjugate prevents aggregation of the particles during formation, thereby resulting in nucleic acid-lipid particles of a homogeneous and defined size containing nucleic acid that is fully encapsulated in the lipid bilayer such that the nucleic acid is completely protected from nuclease degradation. According to the Semple Declaration, this is in stark contrast to the lipoplexes that would be formed based on the cationic liposomes of Choi *et al.*, which contain PEG-ceramide conjugates.

For the foregoing reasons, Sean Semple concludes that it is his opinion that the Choi *et al.* patent does ***not*** teach (or even suggest) the nucleic acid-lipid particles recited in claims 42 and 44-75 because Choi *et al.* do ***not*** teach (or even suggest) (1) nucleic acid-lipid particles, wherein the nucleic acid in the nucleic acid-lipid particles is resistant in aqueous solution to degradation with a nuclease, or (2) methods for making such nucleic acid-lipid particles.

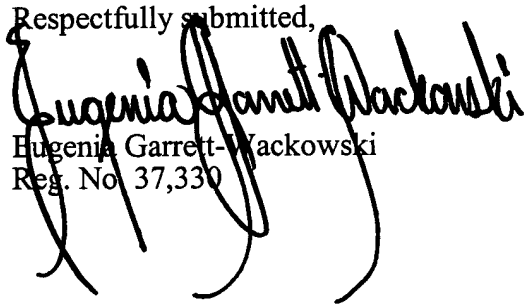
In view of the foregoing remarks, the previously submitted Hope Declaration and the newly submitted Semple Declaration, Choi *et al.*, which discloses methods for preparing and loading classical (or traditional) liposomes, do ***not*** teach the nucleic acid-lipid particles of the present invention, wherein the nucleic acid in the nucleic acid-lipid particles is resistant in aqueous solution to degradation with a nuclease. As Choi *et al.* do ***not*** disclose each and every aspect of the claimed invention, it cannot form the basis of a proper anticipation rejection. Accordingly, the anticipation rejection under 35 U.S.C. § 102(e) over Choi *et al.* is improper and should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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